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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,718	04/19/2001	Lothar Steidler	4779US	3041

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/838,718	STEIDLER ET AL.	
	Examin r	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-12,14-18 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-12,14-18,21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 1, 3, 4, 6-12, 14-18 and 21 are pending examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/03 has been entered.

Applicants' traversal, the amendment to claims 1, 6, 11, 14, and 15, the addition of claim 21, the cancellation of claims 2, 5, and 13, the amendment to the abstract in paper no. 14 is acknowledged and considered.

Priority

This application claims benefit to international application No. PCT/EP99/07800 filed on 10/6/99. Applications that are filed on or after November 29, 2000, and that claim benefit to an earlier-filed international application must include in the first sentence of the specification an indication of whether the international application was published in English under PCT Article 21(2) (regardless of whether the benefit for such application is claimed in an application data sheet). See 37 CFR 1.78(a)(2). The indication, as required by 37 CFR 1.78(a)(2), is missing. Applicant must supply the missing indication as an amendment to the

specification in the reply to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preventing the onset of colitis in a IL10-/- mouse, said method comprising administering a medicament comprising an amount of a cytokine- or cytokine antagonist-producing genetically modified, non-invasive Gram-positive bacteria, wherein the administration of said medicament results in prevention of intestinal mucosal inflammation, and wherein said, does not reasonably provide enablement for a method of preventing IBD in a mammal using the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed method of the instant application embrace a method of preventing inflammatory bowel disease (IBD) in a mammal by administering a cytokine or cytokine-antagonist producing genetically modified Gram positive bacterial strain to the mammal.

The art of record teaches that the etiology of IBD remains poorly understood and several genetic and environmental factors have been implicated in the pathogenesis of IBD (Papadakis et

al. Annu. Rev. Med., Vol. 51, pp.289-298, 2000). The art of record further teaches IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans (Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999).

Furthermore with respect to the animal model (IL10 deficient mice) used in the examples set forth in the disclosure, the state of the art as exemplified by Leach teaches that the role of genetic influences on colitis can potentially be evaluated in IL10 -/- mice (page 127). Leach also teaches that when administering exogenous IL10 was initiated after disease was established at 3 months of age, colitis was ameliorated but not prevented (page 128). It appears from the art of record that IL10 is one factor involved in IBD and in view of the complex nature of IBD, it is not apparent to one skilled in the art how reducing inflammation in IL10 -/- mice reasonably correlates to the method embrace in the claims.

The specification further supports the art of record by stating that, "the cause of IBD is unknown...The pathogenesis of CD and UC probably involves interaction between genetic and environmental factors although no definite etiological agent has been identified so far" (page 4). Thus, the state of the art for preventing IBD in a mammal was considered unpredictable.

The as-filed specification contemplates a cytokine-producing Gram-positive bacterial strain can be used for the preparation of a medicament to treat inflammatory bowel disease. More specifically, the specification specifically teaches a recombinant Lactococcus lactis (L. lactis) comprising a gene encoding an IL-10 protein. The recombinant bacteria are then injected into the peritoneum of healthy mice or mice with induced colitis. The pathology of chronic colitis is characterized by a decrease in colon length and epithelial damage and infiltration of

lymphocytes. Example 2, mice are euthanized and a histological score of the colon demonstrates an increase in colon length of the mice with induced colitis after the treatment with the recombinant IL producing L. lactis compared to mice with induced colitis and untreated and control mice. The specification also demonstrates the prevention of the onset of colitis in IL10-/- mice by intra-gastric inoculation with IL-10 producing L. lactis and 50% reduction of chronic colitis induced by DSS in mice (Example 5, pages 17-18 and Figure 10).

The specification provides sufficient guidance for one skilled in the art to practice a method of preventing the onset of colitis in a IL10-/- mouse using cytokine-or cytokine antagonist producing genetically modified, non-invasive Gram-positive bacteria. However, in view of the In Re Wands Factors, the as-filed specification is not enabled for the full scope of the claimed method. The specification teaches how to prevent onset of colitis in IL10-/- mice using the claimed Gram-positive bacteria. The specification does not provide sufficient guidance for how to reasonably extrapolate from preventing colitis in IL10-/- mice to preventing IBD in a genus of mammals using the claimed methods. The art of record teaches that animal models of intestinal inflammation have opened new avenues for the development and testing of novel therapeutics (Papadakis et al., Annu. Rev. Med., Vol. 51, pages 289-298, 2000, page 289). However, the art of record is absent for teaching how to prevent IBD in a mammal using any type of IBD therapy. In addition, IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans (Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999). In view of the art of record, the as-filed specification does not provide sufficient guidance for one skilled in the art to reasonably correlate from the features observed

with colitis to the features of IBD or Crohn's Disease. The as-filed specification does not provide sufficient guidance or factual evidence to reasonably extrapolate from preventing colitis in experimental mice to preventing IBD in a mammal. Thus, one skilled in the art would not be enabled to practice the full scope of the claimed embodiment.

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the specification to the full scope of the claimed method. Even if a protective response has been shown in IL10-/- mice, it is not apparent as to how the mouse model is reasonably extrapolated to the full breadth of the claimed invention, encompassing any mammal particularly given that there is no evidence showing that the mice model is a general phenomenon, and given the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made provide sufficient guidance and/or evidence to reasonable enable the claimed method for preventing colitis in an IL-10-/- mouse and not the full scope of the claimed method. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of preventing IBD in a mammal and developing effective therapies for preventing IBD in a mammal. In addition, the presence of a working example as provided in the as-filed specification do not reasonably extrapolate to the claimed invention, particularly given that there is no evidence that preventing the onset of colitis in IL10-/- mice can be reasonably extrapolated to preventing IBD in a mammal.

Applicants' arguments filed 1/16/03 have been fully considered but they are not persuasive. The specification teaches how to prevent the onset of colitis in IL10-/- mice using the claimed method, however, the as-filed specification does not provide sufficient guidance or factual evidence for preventing IBD in a mammal. The art of record teaches that IBD is separated into CD and UC and the specification only teaches one skilled in the art how to practice the claimed method to prevent the onset of colitis and not for the full scope of the claimed method. In view of the In Re Wands Factors, the specification does not provide sufficient guidance or factual evidence to reasonably extrapolate from preventing the onset of colitis in IL10-/- mice to preventing IBD in mammals using the claimed method.

With respect to the applicants assertion that the murine model (IL10-/-) is widely accepted by those of ordinary skill in the art as model of treatment of human and other mammals. It is acknowledged that one of skill in the art can treat IBD, however, the specification is absent for sufficient guidance of factual evidence for preventing IBD in a genus of mammals.

The Declaration under 37 CFR 1.132 filed Dr. Steidler is insufficient to overcome the rejection of claim 21 based upon 112 enablement rejection as set forth in the instant Office action because: In view of the reasons set forth above, the as-filed specification does not provide sufficient guidance or factual evidence for one skilled to prevent IBD in a mammal using the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 4, 6-12, 14-18 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation "The method according to claim 2". There is insufficient antecedent basis for this limitation in the claim. The claim depends on a cancelled claim.

Applicant's arguments with respect to claim 18 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 3, 4, 6-12, 14-18, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: where the medicament is being administered. Suggest adding the phrase -- administering a medicament to a mammal with IBD (or susceptible to IBD) -- on line 3 of claims 1 and 21.

Applicant's arguments with respect to claims 1, 3, 4, 6-12, 14-18 and 21 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER